

15°, 20°, 25°, or 30° below the melting temperature of the DNA duplex of sequences of SEQ ID NOS: 1-334, including any range of conditions subsumed within these ranges.

DNA Arrays

[048] In a further embodiment, DNA arrays are used to identify hybridizing sequences from test samples. The term "DNA array" refers to "gene arrays," "DNA chips," "dot array Southern," etc. One of skill in the art will appreciate that an enormous number of array designs are suitable for the practice of this invention. The DNA array will typically include one or a multiplicity of nucleic acid molecules derived from SEQ ID NO: 1 through SEQ ID NO: 327 that specifically hybridize to the nucleic acid expression of which is to be detected. In addition, the array may include one or more control probes to monitor the expression system. Control probes refer to known expression products present at each stage of expression, e.g., ribosomal gene products or the transcripts of other housekeeping genes. The organization of the DNA array will be known to facilitate interpretation of results. Examples in the art describing the uses and composition of DNA arrays can be found in U.S. Patents: 5,700,637, 5,837,832, 5,843,655, 5,874,219, 6,040,138, 6,045,996, and are incorporated by reference.

Molecules That Hybridize to Identified Sequences

[049] Thus, in a particular embodiment, this invention provides an isolated nucleic acid molecule selected from the group consisting of:

- (1) a DNA sequence comprising any one of the sequences presented in SEQ ID NO: 1 through SEQ ID NO: 334;

LAW OFFICES

NNEGAN, HENDERSON,
FARABOW, GARRETT,
& DUNNER, L.L.P.
1300 I STREET, N. W.
WASHINGTON, DC 20005
202-408-4000

- (2) an isolated nucleic acid molecule that hybridizes to either strand of a denatured, double-stranded DNA comprising the nucleic acid sequence of (a) under conditions of moderate stringency; and
- (3) an isolated nucleic acid molecule that hybridizes to either strand of a denatured, double-stranded DNA comprising the nucleic acid sequence of (a) under conditions of high stringency.

[050] As used herein, stringency conditions in nucleic acid hybridizations can be readily determined by those having ordinary skill in the art based on, for example, the length and composition of the nucleic acid. In one embodiment, moderate stringency is herein defined as a nucleic acid having 10, 11, 12, 13, 14, 15, 16, or 17, contiguous nucleotides identical to any of the sequences of SEQ ID NOS: 1-334, or a complement thereof. Similarly, high stringency is hereby defined as a nucleic acid having 18, 19, 20, 21, 22, or more contiguous identical nucleotides, or a longer nucleic acid having at least 80, 85, 90, 95, or 99 percent identity with any of the sequences of SEQ ID NOS: 1-334; for sequences of at least 50, 100, 150, 200, or 250 nucleotides, high stringency may comprise an overall identity of at least 60, 65, 70 or 75 percent.

[051] Generally, nucleic acid hybridization simply involves providing a denatured nucleotide molecule or probe and target nucleic acid under conditions where the probe and its complementary target can form stable hybrid duplexes through complementary base pairing. The nucleic acids that do not substantially form hybrid duplexes are then washed away leaving the hybridized nucleic acids to be detected, typically through detection of an attached detectable label. It is further generally recognized that nucleic acids are denatured by increasing the temperature or decreasing the salt concentration

LAW OFFICES

INNEMAN, HENDERSON,
 FARABOW, GARRETT,
 & DUNNER, L.L.P.
 1300 I STREET, N. W.
 WASHINGTON, DC 20005
 202-408-4000

of the buffer containing the nucleic acids. Under lower stringency conditions (e.g., low temperature and/or high salt) hybrid duplexes (e.g., DNA:DNA, RNA:RNA, or RNA:DNA) will form even where the annealed sequences are not perfectly complementary. Thus specificity of hybridization is reduced at lower stringency. Conversely, at higher stringency (e.g., higher temperature or lower salt) successful hybridization requires fewer mismatches. One of skill in the art will appreciate that hybridization conditions may be selected to provide any degree of stringency.

[052] As used herein, the percent identity between an amino acid sequence encoded by any of SEQ ID NOS: 1-334 and a potential hybridizing variant can be determined, for example, by comparing sequence information using the GAP computer program, version 6.0 described by Devereux et al. (*Nucl. Acids Res.* 12:387, 1984) and available from the University of Wisconsin Genetics Computer Group (UWGCG). The GAP program utilizes the alignment method of Needleman and Wunsch (*J. Mol. Biol.* 48:443, 1970), as revised by Smith and Waterman (*Adv. Appl. Math* 2:482, 1981). The preferred default parameters for the GAP program include: (1) a unary comparison matrix (containing a value of 1 for identities and 0 for non-identities) for nucleotides, and the weighted comparison matrix of Gribskov and Burgess (*Nucl. Acids Res.* 14:6745, 1986), as described by Schwartz and Dayhoff (eds., *Atlas of Protein Sequence and Structure*, National Biomedical Research Foundation, pp. 353-358, 1979); (2) a penalty of 3.0 for each gap and an additional 0.10 penalty for each symbol in each gap; and (3) no penalty for end gaps.

[053] Alternatively, basic protocols for empirically determining hybridization stringency are set forth in section 2.10 of *Current Protocols in Molecular Biology* edited

LAW OFFICES

INNEGAN, HENDERSON,
 FARABOW, GARRETT,
 & DUNNER, L.L.P.
 1300 I STREET, N. W.
 WASHINGTON, DC 20005
 202-408-4000